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Primary Aldosteronism and Obstructive Sleep Apnea: Casual Association or Pathophysiological Link?

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PRIMARY ALDOSTERONISM AND OBSTRUCTIVE SLEEP APNEA: CASUAL ASSOCIATION OR PATHOPHYSIOLOGICAL LINK?

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Abstract:	The coexistence of aldosterone oversecretion and obstructive sleep apnea is frequently observed, especially in patients with resistant hypertension, obesity and metabolic syndrome. Since aldosterone excess and sleep apnea are both independently associated with an increased risk of cardiovascular disease, to investigate whether their coexistence might be attributed to common predisposing conditions, such as metabolic disorders, or to an actual pathophysiological interconnection appears of great importance. Fluid overload and metabolic abnormalities relating to aldosterone oversecretion may be implicated in obstructive sleep apnea development. Nocturnal intermittent hypoxia may in turn exacerbate renin-angiotensin-aldosterone system activity, thus leading to hyperaldosteronism. Furthermore, fat tissue excess and adipocyte secretory products might predispose to both sleep apnea and aldosterone oversecretion in subjects with obesity. Consistent with these evidences, obstructive sleep apnea frequently affects patients with primary aldosteronism. Conversely, whether primary aldosteronism is more prevalent in individuals affected by obstructive sleep apnea compared to the general population remains controversial.

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1 PRIMARY ALDOSTERONISM AND OBSTRUCTIVE SLEEP APNEA: CASUAL
2 ASSOCIATION OR PATHOPHYSIOLOGICAL LINK?

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Abstract

The coexistence of aldosterone oversecretion and obstructive sleep apnea is frequently observed, especially in patients with resistant hypertension, obesity and metabolic syndrome. Since aldosterone excess and sleep apnea are both independently associated with an increased risk of cardiovascular disease, to investigate whether their coexistence might be attributed to common predisposing conditions, such as metabolic disorders, or to an actual pathophysiological interconnection appears of great importance. Fluid overload and metabolic abnormalities relating to aldosterone oversecretion may be implicated in obstructive sleep apnea development. Nocturnal intermittent hypoxia may in turn exacerbate renin-angiotensin-aldosterone system activity, thus leading to hyperaldosteronism. Furthermore, fat tissue excess and adipocyte secretory products might predispose to both sleep apnea and aldosterone oversecretion in subjects with obesity. Consistent with these evidences, obstructive sleep apnea frequently affects patients with primary aldosteronism. Conversely, whether primary aldosteronism is more prevalent in individuals affected by obstructive sleep apnea compared to the general population remains controversial.

44 Introduction

45 Obstructive sleep apnea (OSA), aldosterone excess and resistant hypertension (RH) are common
46 comorbidities, especially in patients affected by obesity[1]. The prevalence of OSA is high in patients
47 affected by RH and even higher in individuals with hypertension refractory to medical therapy[2]. In
48 patients with RH, oversecretion of aldosterone is a frequent finding and primary aldosteronism (PA)
49 has a significantly higher prevalence compared with the general hypertensive population[3]. Patients
50 with RH are significantly more likely to experience adverse cardiovascular outcomes, such as stroke,
51 myocardial infarction, heart failure, renal failure and death, compared with subjects with nonresistant
52 hypertension[4]. Studies performed in the last years suggest that PA is frequent in patients with
53 OSA[5,6] and, on the basis of these evidences, the 2016 Endocrine Society Guideline recommends
54 to screen for PA all patients with hypertension and OSA[7]. The impact of aldosterone excess and
55 sleep apnea on the cardiovascular morbidity and mortality of patients with hypertension is of great
56 importance, as well as the recognition of the interplay between these conditions. Previous studies
57 hypothesized that a bidirectional relationship between aldosterone levels and OSA might be present
58 in patients with RH and PA[8]. Nevertheless, whether the association between PA and OSA is
59 accidental or pathophysiologically-based remains controversial.

61 Epidemiology

62 1.Primary aldosteronism

63 PA is mostly sporadic, due to unilateral aldosterone-producing adenoma (APA) or bilateral
64 hyperaldosteronism (BHA), and less frequently (1-6%) is a familial condition[9]. Individuals with
65 PA show an increased risk of stroke, coronary artery disease, heart failure, atrial fibrillation, left
66 ventricular hypertrophy, kidney damage, diabetes and metabolic syndrome compared to patients with
67 essential hypertension[10, 11]. The prevalence of PA rates between 5.9% in the general hypertensive
68 population[12] and 11.2% in patients from referral centers[13], and progressively increases with
69 hypertension severity[12].

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70 Two prospective studies suggested a high prevalence of aldosterone excess in patients with sleep
71 disordered breathing (SDB). Calhoun et al. showed that autonomous aldosterone secretion was more
72 frequently observed in patients with RH at high risk of OSA (36%) compared with low-risk patients
73 (19%), defined according to the Berlin Questionnaire results[5]. However, OSA diagnosis was not
74 confirmed by polysomnography and patients with aldosterone oversecretion did not underwent
75 confirmatory testing for PA diagnosis. Di Murro et al. reported a 34% prevalence of PA in patients
76 affected by hypertension and OSA[6]. Nonetheless, polysomnography was performed only in patients
77 showing excessive daytime sleepiness, thus leading to diagnosis of OSA only in a selected subgroup
78 of symptomatic individuals. Therefore, it cannot be excluded that PA prevalence among the overall
79 symptomatic and asymptomatic OSA population would have been different.

80 The recent multicenter multi-ethnic cross-sectional HYPNOS study, reported an 8.9% prevalence of
81 PA in a population of 203 patients with OSA (102 Caucasians and 101 Chinese)[14], a figure that
82 does not significantly differ from the 5.9-11.2% prevalence observed in the PATO and PAPY studies,
83 respectively[12,13]. Moreover, a sub-analysis performed to identify PA prevalence in patients in
84 whom OSA was the only indication to proceed to PA screening, showed that only 1/63 (1.5%) patients
85 displayed confirmed PA. These results provocatively challenge the current Endocrine Society
86 Guideline recommendation to screen for PA all patients affected by OSA and arterial hypertension,
87 irrespective of hypertension severity and the presence of other risk factors.

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89 2.Obstructive sleep apnea

90 OSA is a chronic sleep disorder characterized by recurrent episodes of complete (apneas) or partial
91 airflow cessation (hypopneas) due to obstruction of the upper respiratory tract, leading to intermittent
92 hypoxia, hypercapnia and sleep arousals[15]. OSA is an independent risk factor for hypertension[16-
93 18] and cardiovascular disease [19,20], and a predictor of cardiovascular outcomes, including sudden
94 cardiac death[21]. OSA is frequently diagnosed in patients with various cardiovascular comorbidities,
95 such as stroke, end-stage chronic kidney disease, ischemic cardiomyopathy, heart failure, atrial

fibrillation and hypertrophic cardiomyopathy[15]. The prevalence of OSA in the overall adult population varies from 9% to 38%, ranging between 13% to 33% in men and 6% to 19% in women[22]. Advanced age is associated with an elevated prevalence of OSA, up to 90% for all stages in a cohort of elderly men[22,23]. OSA prevalence is high in patients with obesity or metabolic syndrome, ranging from 50% to 60%, and it is even higher in subjects with morbid obesity and diabetes[24]. The prevalence of OSA in patients with hypertension is reported to be 30% to 50%[25] and it has been assessed to be as high as 92%[26] for all stages and 70% for severe OSA[27] in patients with RH. A recent study displayed an even higher prevalence of moderate OSA (95.2%), severe OSA (64.3%) and OSA syndrome (52.4%) in patients with refractory hypertension[2].

Some studies showed that OSA is more frequent in patients with than in those without PA. In a retrospective cohort, OSA prevalence was significantly higher in subjects with autonomous aldosterone secretion (18%) compared with patients without it (9%)[28]. However, the lack of PA confirmatory testing and the identification of OSA patients using database records are the major limitations of this study. Indeed, the prevalence of OSA in both PA and non-PA hypertensive patients resulted even lower than the one observed in the general population[22]. In a prospective study, the reported OSA prevalence was 78.1% and 71.0% in patients affected by RH with and without PA, respectively, and OSA severity was shown to be higher in the former group[29]. In a recent study aimed at exploring the effects of PA treatment on OSA severity, a 79% prevalence of OSA was showed in patients with PA[30]. Nevertheless, it should be noted that the study cohort was selected by the presence of at least one risk factor for sleep apnea, such as male gender, obesity, history of snoring or daytime sleepiness, therefore the assessed prevalence might represent an overestimation of the actual OSA prevalence in the overall PA population because of selection bias. In the HYPNOS study, among 207 patients with a confirmed diagnosis of PA, the prevalence of OSA was 67.6%[14].

3.Ethnic differences in primary aldosteronism and obstructive sleep apnea prevalence

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Whether ethnic differences might affect the risk of both OSA and PA onset has been a matter of debate. The prevalence of OSA in the general Caucasian population was estimated to be as high as 38% to even more than 90% in selected cohorts[2,22,23] and it was observed to be 64.4% in patients with PA[14]. The prevalence of PA was found to be 5.9% in the general hypertensive population[12] and 11.8% in Caucasian patients with OSA[14].

The SDB risk in Asian patients was reported to be higher than in Caucasians[31]. OSA is more frequent in Chinese men than in women, although prevalence discrepancies lower along with age[32,33]. The elevated SDB risk in Asians may be correlated to anatomical factors, such as the higher frequency of craniofacial skeletal anomalies and the different body fat distribution compared to Caucasians[31]. Asian patients usually display a greater dietary salt intake than Caucasians, and this feature, along with an elevated salt-sensitivity of blood pressure, might contribute to hydrosaline retention and pharyngeal edema[34]. In the HYPNOS study, Chinese patients with PA had a 70% prevalence of OSA, which was not significantly different compared with Caucasians[14], and resulted to be similar to that reported in Chinese with essential hypertension[35]. Moreover, aldosterone positively correlated with apnea-hypopnea index (AHI) in Caucasians with PA, but not in Chinese patients[14]. Hence, it is reasonable to suppose that the pathophysiology of OSA in Asians might be related mostly to anthropomorphic predisposing features and high salt intake than to aldosterone-mediated mechanisms.

Current evidences suggest that SDB risk is greater among patients of African descent compared to Caucasians[31,36,37]. SDB predisposition might be correlated to obesity influence and presence of enlarged upper airway soft tissue in blacks, as well as frequent disadvantageous socio-environmental conditions and tobacco smoke[31]. Blacks with hypertension tend to have lower plasma renin activity than whites[38], possibly suggesting a greater frequency of aldosterone-dependent hypertension [3], though no differences in PA prevalence have been observed[3,39]. Moreover, blacks tend to be more salt-sensitive and to display lower responsiveness to angiotensin-converting enzyme inhibitors and beta-blockers compared to whites[40]. These evidences possibly suggest that aldosterone excess

might play a relevant role in the pathophysiology of OSA in African-Americans, as supported by a study reporting a higher prevalence of both OSA and PA compared with Caucasians, Hispanics, and Asians[28].

The pathophysiological link between aldosterone and OSA

1. Obstructive sleep apnea effects on the renin-angiotensin-aldosterone system

Several pathophysiological mechanisms relating OSA to hypertension have been proposed, including intermittent hypoxia, hypercapnia, intrathoracic negative pressure changes and nocturnal arousals. Blood pressure increase due to intermittent hypoxic events has been associated to sympathetic nervous system hyperactivity, renin-angiotensin-aldosterone system (RAAS) overstimulation, oxidative stress, endothelial dysfunction, endothelin overproduction and pro-inflammatory state[41]. OSA severity might correlate with aldosterone oversecretion, thus leading to water and sodium retention, and subsequent rise in blood pressure. Indeed, patients with OSA and RH with normal plasma renin activity, plasma aldosterone concentration and aldosterone-to-renin ratio displayed a reduced aldosterone response to saline load along with increasing severity of OSA[42].

Is aldosterone excess a result of RAAS hypoxia-induced activation in patients with OSA, or does it represent a contributing factor to OSA pathophysiology? To assess causality of OSA and aldosterone excess relationship, a number of clinical studies were performed and evaluated the impact of continuous positive airway pressure (CPAP) treatment on aldosterone levels in patients with OSA. The results of a meta-analysis of 5 studies indicated minimally yet significantly reduced aldosterone levels after at least one month of CPAP therapy. Nonetheless, a sub-analysis including only randomized controlled trials indicated no significant aldosterone changes in the CPAP-treated patients compared to controls[43]. However, the study performed by Møller et al., showing no significant decrease of aldosterone levels after CPAP therapy, might be limited by the lack of an appropriate BMI-matching of enrolled subjects, thus leading to biased results due to obesity influence

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3 172 on CPAP effects[44]. Of interest, all included studies were performed in Europe and enrolled patients
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5 173 were predominantly male, thus ethnicity and gender influence on aldosterone response to CPAP
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11 175 A recent study showed that also short-term CPAP treatment might be able to lower plasmatic
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18 178 night during the entire 6-month study period - significantly decreased urinary aldosterone excretion
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20 179 in RH patients with moderate-severe OSA compared to controls[46]. Another study displayed that
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22 180 CPAP therapy was able to significantly decrease aldosterone levels and blood pressure in OSA
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24 181 patients with day-and-night sustained hypertension compared to controls, but not in those with
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27 182 isolated nocturnal hypertension[47]. Lastly, aldosterone levels were not significantly decreased by
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29 183 angiotensin receptor-blocker treatment in a cohort of subjects with hypertension and OSA compared
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31 184 to those without OSA, while add-on CPAP therapy in the former group tended to lower aldosterone
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36 186 hyperaldosteronism in patients with hypertension and OSA[48].
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38 187 39 40 41 188 **2.Overnight rostral fluid shift as a pathogenetic feature predisposing to obstructive sleep apnea**

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43 189 Several evidences support the importance of volume overload and nocturnal rostral fluid shift in the
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45 190 pathogenesis of OSA. This latter phenomenon is due to redistribution of fluid, accumulated during
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50 192 displacement into neck structures promotes upper respiratory tract soft tissue edema, which in turn
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52 193 causes airway resistance increase and airflow obstruction[49].
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55 194 Targeting fluid overload in hypervolemic patients might be effective to reduce AHI and upper airway
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57 195 collapsibility in subjects with OSA[49]. A 2-week course of intensified diuretic treatment was
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3 196 reported to be effective in improving OSA severity in patients with uncontrolled hypertension and
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8 198 Aldosterone excess, along with increased dietary sodium intake, leads to fluid overload[1,51]. A
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10 199 meta-analysis showed that aldosterone and angiotensin II are significantly higher in OSA-affected
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12 200 patients with hypertension than in normotensive individuals[52]. Therefore, it has been hypothesized
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14 201 that aldosterone excess might be implicated in volume overload predisposing nocturnal rostral fluid
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17 202 shift in patients with OSA[51]. Conversely, in a large cross-sectional study plasma aldosterone levels
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19 203 and plasma renin activity were not significantly different in RH patients with no or mild OSA
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21 204 compared with patients with moderate-severe OSA[53].
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26 206 **3.Aldosterone blockade and obstructive sleep apnea**

28 207 Several studies documented a positive correlation between aldosterone levels and OSA severity.
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30 208 Plasma and urinary aldosterone levels significantly correlated with AHI in subjects with RH, but this
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33 209 correlation was not observed in normotensive individuals nor in patients with treatment-controlled
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35 210 hypertension of similar age, BMI and OSA severity[46,54]. Nevertheless, a study reported a positive
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37 211 correlation between aldosterone levels and AHI in patients affected by essential, but not secondary,
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40 212 RH[29]. Some studies reported that plasma and urinary aldosterone levels positively correlate with
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42 213 AHI in patients with RH and autonomous aldosterone production. Conversely, no significant
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44 214 correlation between aldosterone levels and AHI was observed in patients with normal aldosterone
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47 215 secretion, suggesting that the role of aldosterone in OSA pathogenesis and severity might be relevant
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49 216 only in subjects displaying a status of aldosterone excess[55,56].
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51 217 A number of clinical studies evaluated the effect of aldosterone blockade on airway obstruction. Two
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53 218 small observational studies reported a significant reduction of AHI after a 2-month treatment with
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56 219 spironolactone in patients with RH and moderate-severe OSA[57], and a 3-month treatment with
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58 220 eplerenone in patients with essential RH and OSA, respectively[58]. Likewise, a small randomized
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60 221 blank-controlled prospective trial showed a significant reduction of OSA severity, blood pressure and

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aldosterone levels in patients affected by RH and moderate-severe OSA after a 3-month
spironolactone therapy on top of preexisting antihypertensive treatment compared to controls[59].
Furthermore, AHI and neck circumference were reduced by PA medical or surgical therapy in patients
affected by both PA and OSA[30].
Aldosterone excess might concur to airway obstruction pathogenesis not only by fluid overload-
mediated mechanisms, but also through direct impairment and deregulation of central ventilatory-
control[41,60]. Nowadays, targeting aldosterone excess has not yet been defined as an effective
treatment for patients with OSA. Notwithstanding, mineralocorticoid receptor-antagonist treatment
should be considered in patients with OSA and RH[41].

4.Primary aldosteronism, obstructive sleep apnea and obesity

The coexistence of high aldosterone levels and OSA might also be attributed to the presence of
common predisposing conditions, such as obesity and metabolic disorder[61]. OSA prevalence is
elevated in individuals affected by obesity or metabolic syndrome, and it is even higher in subjects
with diabetes and morbid obesity[24]. Furthermore, OSA is associated with insulin resistance
independently of concomitant obesity[62] and abnormal glucose metabolism may be attributed to
hypoxemia-induced sympathetic nervous system and RAAS activation[63]. Diabetic neuropathy may
in turn affect central control of respiration promoting sleep apnea development, leading to a vicious
cycle[64].

Obesity is common in patients with both OSA and RH[1]. Interestingly, aldosterone levels appear to
be higher in patients with OSA and metabolic syndrome compared to those without metabolic
alterations[65]. Several studies observed high aldosterone levels in obese subjects, especially in those
with visceral obesity[66]. Both adolescents and women with obesity displayed significantly higher
aldosterone levels than lean individuals, and weight loss led to significant aldosterone
reduction[67,68]. A recent study demonstrated that urinary aldosterone levels were positively
correlated with BMI in RH patients, especially in men and regardless of ethnicity[69]. Moreover,

BMI was directly correlated to aldosterone levels in postmenopausal Chinese women with obesity and hypertension but not in premenopausal women, possibly because of the role of endogenous estrogens as a regulator of aldosterone secretion before menopause[70].

The pathophysiological pathways linking obesity to aldosterone excess still have to be fully elucidated. Adipose cells are able to produce angiotensinogen and angiotensin II; studies on animal models showed that angiotensinogen might be released into circulation by adipose tissue and its levels might correlate with systolic blood pressure[71]. Animal model studies suggested that high concentrations of fatty acids in portal venous blood of obese individuals might be metabolized by the liver to oxidized products, such as linoleic acid derivatives, which could stimulate aldosterone secretion[72]. Adipocyte secretory products, such as adipokines and adipocyte-derived hormones, may directly stimulate adrenocortical aldosterone secretion, independent of angiotensin II[73]. Complement-C1q TNF-related protein-1 (CTRP1) was found to be overexpressed in both patients with obesity and hypertension, and to act as an endogenous aldosterone-stimulating factor[74]. Other adipokines such as tumor necrosis factor- α and interleukin-6 have also been shown to be involved in aldosterone secretion[75]. *In vitro* and *in vivo* studies on animal models showed that the adipocyte-derived anorectic hormone leptin could directly promote aldosterone secretion independently of potassium, angiotensin II and adrenocorticotrophic hormone levels[75,76]. Recent findings suggest that leptin-mediated pathway leading to hypertension development in patients with obesity might be mostly dependent to aldosterone oversecretion in women, and predominantly related to hypothalamic receptor activation and consequent sympathetic nervous system stimulation in men[77]. Interestingly, the role of obesity in the pathogenesis of aldosterone hypersecretion appeared to be relevant in patients with BHA, but not with APA[78,79]. These observations suggest that, while aldosterone overproduction is determined by a hormone-secreting tumor in APA patients, obesity might play an important role in aldosterone excess by adipokine-driven pathways in subjects with BHA[78,79].

Vice versa, aldosterone excess might contribute to obesity development through adipose tissue maturation by means of mineralocorticoid receptor activation, thereby leading to a vicious cycle[80].

Higher prevalence of metabolic syndrome and diabetes has been shown in patients with PA compared with essential hypertension[81]. Insulin secretion might be impaired by either aldosterone-induced hypokalemia, and direct aldosterone effects resulting in pancreatic beta-cell dysfunction and apoptosis. Furthermore, hyperaldosteronism-related insulin resistance might be explained by defective expression of glucose transporter 4, insulin receptor and its related signal transducing factors in skeletal muscle and adipose tissue, as well as increased hepatic gluconeogenesis and endothelial remodeling affecting insulin and glucose peripheral delivery[82]. Finally, recent findings support the coexistence of mild glucocorticoid excess and aldosterone overproduction in PA, suggesting a role for cortisol-driven pathways in the determination of metabolic risk in a proportion of patients with PA[83].

Conclusions

Aldosterone excess, OSA and obesity could be interconnected within the context of metabolic syndrome through vicious cycle pathogenetic mechanisms. Obesity leads to OSA development through fat deposition within the neck, while OSA could in turn promote obesity. Adipokines released by visceral fat might induce aldosterone overproduction, which could in turn stimulate fat cell differentiation. Moreover, aldosterone excess-induced volume overload contributes to OSA pathogenesis, and intermittent hypoxia might in turn exacerbate RAAS activation. OSA and hyperaldosteronism might both lead to oxidative stress and inflammation, thus favoring the production of oxidized lipidic derivatives which could in turn aggravate aldosterone oversecretion[72]. Furthermore, hyperaldosteronism-related glucose metabolism dysregulation and diabetes[82] might lead to diabetic neuropathy development, which may consequently affect upper airway neural reflexes, thus favoring OSA[64]. Consistent with these evidences, OSA is frequently observed in patients with PA. Conversely, whether PA is more prevalent in patients with OSA compared with the general population remains controversial.

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